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I, the undersigned being an officer duly authorized in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is the true copy of the ***Application and Provisional Specification*** *filed in connection with* ***Patent Application No. 1098/Del/2005 dated 03rd May, 2005.***

Witness my hand this 28th day of November 2006

(DR. K.S. KARDAM)
Assistant Controller Of Patents & Designs

1098-DEL-05

03 MAY 2005

FORM 1 THE PATENT ACT 1970 (39 of 1970) & The Patents Rules, 2003 APPLICATION FOR GRANT OF PATENT (See section 7, 54 and 135 and Rule 20(1))	(FOR OFFICE USE ONLY) Application No._____ Filing Date:_____ Amount of Fee Paid: Rs._____ CBR No. _____ Signature: _____

1. APPLICANT (S)
RANBAXY LABORATORIES LIMITED, an Indian Company, incorporated under the Companies Act, 1956, Head Office at 12th Floor, Devika Tower, 6, Nehru Place, New Delhi-110019, India.

2. INVENTOR (S)
VENKATA P. PALLE, ASHWANI KUMAR VERMA, SANJAY MALHOTRA, ABHIJIT RAY, GEETA SHARMA
All Indian Nationals, of Ranbaxy Laboratories Limited, Plot No. 20, Sector – 18, Udyog Vihar Industrial Area, Gurgaon – 122001, Haryana, India.

3. TITLE OF THE INVENTION
"TRIAZOLONE DERIVATIVES AS ANTI-INFLAMMATORY AGENTS"

4. ADDRESS FOR CORRESPONDENCE OF APPLICANT/ AUTHORIZED AGENT IN INDIA:
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5. PRIORITY PARTICULARS OF THE APPLICATION(S) FILED IN CONVENTION COUNTRY: NOT APPLICABLE

6. PARTICULARS FOR FILING PATENT COOPERATION TREATY (PCT) NATIONAL PHASE APPLICATION: NOT APPLICABLE

7. PARTICULARS FOR FILING DIVISIONAL APPLICATION: NOT APPLICABLE

8. PARTICULARS FOR FILING PATENT OF ADDITION: NOT APPLICABLE

9. DECLARATIONS:

10.

(i) **Declaration by the Inventor(s):**

We, the above named inventor(s) is/are the true and first inventor(s) for this invention and declare that the applicant herein, **Ranbaxy Laboratories Limited**, Head Office at 12th Floor, Devika Tower, 6, Nehru Place, New Delhi-110019, India, is our assignee or legal representative.

Date	Signature(s)	Name (s)
_____	_____	**Venkata P. Palle**
2-5-05		**Ashwani Kumar Verma**
02-05-2005	Sanjay Malhotra	**Sanjay Malhotra**
_____	_____	**Abhijit Ray**
_____	_____	**Geeta Sharma**

(ii) **Declaration by the applicant(s) in the convention country:**

We, the applicant, in the convention country declare that the applicant herein is our assignee or legal representative.

For Ranbaxy Laboratories Limited

Date : _____

(SUSHIL KUMAR PATAWARI)
Company Secretary

(iii) **Declaration by the Applicant(s) :**

We, the applicant (s) hereby declare (s) that :-

- ◊ We are in possession of the above-mentioned invention.
- ◊ The provisional / complete specification relating to the invention is filed with this application.
- ◊ The invention as disclosed in the specification uses the biological material from India and necessary permission from the competent authority shall be submitted by us before the grant of the patent to us.
- ◊ There is no lawful ground of objection to the grant of the Patent to us.
- ◊ We are the assignee or legal representative of true and first inventors.
- ◊ The application or each of the applications, particulars of which are given in Para-5 was the first application in convention country / countries in respect of our invention.
- ◊ We claim the priority from the above mentioned application(s) filed in convention country/ countries and state that no application for protection in respect of the invention had been made in a convention country before that date by us or by any person from which we derive the title.
- ◊ Our application in India is based on International application under Patent Cooperation Treaty (PCT) as mentioned in Para-6.
- ◊ The application is divided out of our application particulars of which are given in Para-7 and pray that this application may be treated as deemed to have been filed on _____ under sec.16 of the Act.
- ◊ The said invention is an improvement in or modification of the invention particulars of which are given in Para-8.

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10. **FOLLOWING ARE THE ATTACHMENTS WITH THE APPLICATION:**

(a) Provisional specification / Complete specification
(b) Complete specification (in conformation with the international applications)/as amended before the International Preliminary Examination Authority (IPEA), as applicable (2 copies), No. of Pages _____ No. of claims _____.
(c) Drawings (in conformation with the international application)/as amended before the International Preliminary Examination Authority (IPEA), as applicable (2 copies), No. of sheets _____.
(d) Priority documents
(e) Translation of priority documents / Specification/International Search Report
(f) Statement and undertaking on Form 3
(g) Power of Authority
(h) Declaration of inventorship on Form 5
(i) Sequence listing in electronic form
(j) _____

Fee Rs. _____ _____in Cash/Cheque/Bank Draft bearing No. _____

Date _____ on HDFC Bank Limited, Gurgaon.

We hereby declare that to the best of our knowledge, information and belief the fact and matters stated herein are correct and we request that a patent may be granted to us for the said invention.

Dated this 2ND day of May, 2005.

For Ranbaxy Laboratories Limited

(SUSHIL KUMAR PATAWARI)
Company Secretary

To

The Controller of Patent
The Patent Office
New Delhi

1098/DEL/05

FORM 2

The Patents Act, 1970

(39 of 1970)

&

The Patent Rules, 2003

PROVISIONAL SPECIFICATION

(See Section 10)

TRIAZOLONE DERIVATIVES AS ANTI-INFLAMMATORY AGENTS

RANBAXY LABORATORIES LIMITED
HEAD OFFICE: 12TH FLOOR, DEVIKA TOWER, 06 NEHRU PLACE,
NEW DELHI-110019

(A Company incorporated under the Companies Act, 1956)

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed

FIELD OF THE INVENTION

The present invention relates to novel triazolone derivatives as anti-inflammatory agents.

The compounds of this invention can be useful for inhibition and prevention of inflammation and associated pathologies including inflammatory and autoimmune diseases such as sepsis, rheumatoid arthritis, inflammatory bowel disease, type-1 diabetes, asthma, chronic obstructive pulmonary disorder, organ transplant rejection and psoriasis.

This invention also relates to pharmacological compositions containing the compounds of the present invention and the methods of treating sepsis, rheumatoid arthritis, inflammatory bowel disease, type-1 diabetes, asthma, chronic obstructive pulmonary disorder, organ transplant rejection and psoriasis, and other inflammatory and/or autoimmune disorders, using the compounds.

BACKGROUND OF THE INVENTION

During the last decade, numerous studies have focused on the roles played by cytokines, a unique class of ontracellular regulatory proteins, in the pathogenesis of many diseases. Cytokines play a crucial role in initiating, maintaining, and regulating immunological and inflammatory processes. Advances in our understanding of their role in immune and inflammatory disorders have led to the development of cytokine-based therapies-that is, therapies that aim to inhibit or restore the activity of specific cytokines. Today, drugs that block inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), are among the most successful agents being introduced to the market.

Elevated levels of proinflammatory cytokines viz TNF-α and IL-1β are associated with the pathogenesis of many immune mediated inflammatory disorders like sepsis, rheumatoid arthritis, inflammatory bowel disease, type-1 diabetes, asthma, chronic obstructive pulmonary disease, organ transplant rejection and psoriasis. Inflammation is regulated by a large number of pro- and anti-inflammatory mediators, which include cytokines, eicosanoids, nitric oxide, and reactive oxygen species. The central role of these inflammatory mediators in the pathogenesis of both chronic and acute inflammatory diseases is well documented. Until a few years ago, inflammatory disorders were treated primarily with relatively non-selective anti-inflammatory agents, such as corticosteroids and various non-steroidal anti-inflammatory

drugs. In recent years, novel therapies have been developed that specifically interfere with the action of selected pro-inflammatory mediators, such as TNF-α and PGE-2. These specific anti-inflammatory therapies have already proven to be very successful in the treatment of rheumatoid arthritis, inflammatory bowel disease, and several other inflammatory diseases.

The development of protein-based therapies that inhibit the activities of tumor necrosis factor-alpha (TNF-α), including etanercept (Enbrel; Amgen/Wyeth), infliximab (Remicade; Centocor), and adalimumab (Humira; Abbott), has been an important advancement in the treatment of autoimmune diseases such as rheumatoid arthritis. The approval of Kineret - an interleukin-1 (IL-1beta) receptor antagonist - further indicates the clinical activity of protein-based therapies that regulate cytokine activities. However, current injectable therapies have associated limitations and risks, including the potential for increased malignancies and infections and increased congestive heart failure. Studies in rodent models have provided evidence that targeting specific pathways involved in TNF-α activities are effective approaches to interrupting the pro-inflammatory process. Oral small molecules that regulate these pathways should be the next significant advancement in the treatment of chronic inflammatory diseases when used either as a monotherapy or in combination with the current injectables.

Numerous studies have now clearly established that the pathogenesis of inflammatory diseases requires cytokine-mediated communication between endothelial cells, infiltrating leukocytes, resident macrophages, mast cells, epithelial cells and osteoclasts. The p38 mitogen activated protein kinase (p38 MAPK) regulates cytokine levels and therefore plays a central role in both the cellular infiltration and activation responses associated with inflammatory diseases.

The p38 MAPK is a member of a large family of MAPK's whose signalling pathways also include the extracellular regulated kinases (ERK) & the c-jun N terminal kinases (JNK). MAP kinases are Serine Threonine Kinases that transduce environmental stimuli to the nucleus and they themselves are activated by upstream MAPK kinases by phosphorylation on both Tyrosine and Threonine residues. The MAPK pathways are involved in alterations in cell physiology resulting from a variety of stimuli and control cell death, cell cycle machinery, gene transcription and protein translation. p38α MAPK was first identified as a

tyrosine phosphorylated protein in LPS (Lipopolysaccharide) stimulated macrophages. The human p38α MAPK was identified as the target of pyridinyl imidazole compounds (cytokine suppressive anti-inflammatory drugs) that were known to block TNF-α and IL-1 release from LPS stimulated monocytes. After the cloning of first p38 MAPK (p38α), additional members of the p38 MAPK family were cloned by homology, including the p38α, p38β and p38γ.

The p38 pathway controls the activity of multiple transcription factors and the expression of many genes. There is ample evidence implicating a pivotal role for p38 in inflammatory processes mediated by IL-1 and TNF-α. p38 inhibitors have been shown to effectively block both TNF-α and IL-1 biosynthesis by LPS stimulated human monocytes.
In addition, p38 MAPK also plays a role in the production of IL-4, IL-6, IL-8 and IL-12. p38 MAPK is also critical for cell response to certain cytokines. Treatment of human neutrophils with GM-CSF, TNF-α or TGF-α results in p38 activation. GM-CSF and
TNF-α are potent enhancers of neutrophil respiratory activity suggesting a role for p38 MAPK in respiratory burst.

p38 has also been implicated in the induction of cyclooxygenase-2 (COX-2) in LPS induced monocytes. COX-2 enzyme is the key enzyme in the production of prostaglandins from arachidonic acid. Inhibitors of p38 MAP kinase are also expected to inhibit COX-2 expression. Accordingly inhibitors of cytokine synthesis would be expected to be effective in disorders currently treated with NSAID's. These disorders include acute and chronic pain as well as symptoms of inflammation and cardiovascular disease.

Compounds, which modulate release of one or more of the aforementioned inflammatory cytokines, can be useful in treating diseases associated with the release of these cytokines.

US patent number 5,681,841 discloses cyclic urea derivatives, pharmaceutical compositions containing these compounds and process for preparing them. US patent number 6,528,957 discloses N-aryl-1,2,4-triazolin-5-one derivatives. WO94/11357 discloses process for the preparation of triazolone compounds. WO00/59506 discloses heterocyclic containing biphenyl derivatives useful for the treatment of diabetes and related disorders and method of preparing them. WO 97/03067 discloses piperazine derivatives as therapeutic agents. CA

2,197,789 discloses cyclic urea derivatives, pharmaceutical compositions containing these compounds and process for preparing them.

SUMMARY OF THE INVENTION

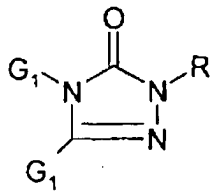
The present invention provides novel triazolone derivatives, which can be used for the inhibition and prevention of inflammation and associated pathologies such as sepsis, rheumatoid arthritis, inflammatory bowel disease, type-1 diabetes, asthma, chronic obstructive pulmonary disorder, organ transplant rejection and psoriasis.

Pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers or N-oxides of these compounds having the same type of activity are also provided.

Pharmaceutical compositions containing the compounds, and which may also contain pharmaceutically acceptable carriers or diluents, which may be used for the treatment of inflammatory and autoimmune diseases such as sepsis, rheumatoid arthritis, inflammatory bowel disease, type-1 diabetes, asthma, chronic obstructive pulmonary disorder, organ transplant rejection and psoriasis.

Other aspects will be set forth in accompanying description which follows and in part will be apparent from the description or may be learnt by the practice of the invention.

In accordance with one aspect, there is provided a compound having the structure of Formula I



Formula I

and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers diastereomers, N-oxides, polymorphs, metabolites;

wherein

G_1 is independently selected from the group consisting of aryl or heteroaryl;

R is alkyl, cycloalkyl, heteroaryl, heterocyclyl, aryl, cycloalkylalkyl, heterocyclylalkyl, heteroarylalkyl, $-(CH_2)_gCONR_xR_y$;

g is an integer selected from 1-3;

R_x and R_y are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, aralkyi, $-SO_nR_1$ (wherein n is 0, 1 or 2), heteroaryl, heterocyclyl, heteroarylalkyl or heterocyclylalkyl;

R_1 is hydrogen, alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, heterocyclylalkyl or heteroarylalkyl;

In accordance with second aspect, there is provided a method for the treatment of mammal suffering from inflammation and associated pathologies.

In accordance with third aspect, there is provided a method for the treatment of mammal suffering from inflammatory diseases and associated pathologies including sepsis, rheumatoid arthritis, inflammatory bowel disease, type-1 diabetes, asthma, chronic obstructive pulmonary disorder, organ transplant rejection and psoriasis.

In accordance with fourth aspect, there are provided a pharmaceutical compositions containing the compounds, and which may also contain pharmaceutically acceptable carriers or diluents, which may be used for the treatment of inflammatory and autoimmune diseases such as sepsis, rheumatoid arthritis, inflammatory bowel disease, type-1 diabetes, asthma, chronic obstructive pulmonary disorder, organ transplant rejection and psoriasis.

In accordance with fifth aspect, there is provided a process for the preparation of compounds disclosed herein.

In accordance with sixth aspect, the compounds of the present invention are screened as p38 MAP Kinase inhibitors.

The following definitions apply to terms as used herein:

The term "alkyl" unless and otherwise specified refers to a monoradical branched or unbranched saturated hydrocarbon chain having from 1 to 20 carbon atoms. This term is exemplified by groups such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, t-butyl, n-hexyl, n-decyl, tetradecyl, and the like.

It may further be substituted with one or more substituents selected from the group consisting of alkenyl, alkynyl, alkoxy, cycloalkyl, acyl, acylamino, acyloxy, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, thiocarbonyl, substituted thiocarbonyl, carboxy, $-COOR_2$ (wherein R_2 is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroarylalkyl or heterocyclylalkyl), thiol, aryloxy, alkoxyamino, $-NR_xR_y$, $-C(=O)NR_xR_y$, $-OC(=O)NR_xR_y$, $-NHC(=O)NR_xR_y$, (wherein R_x and R_y are the same as defined earlier), nitro, $-S(O)_nR_1$ (wherein n and R_1 are the same as defined earlier). Unless otherwise constrained by the definition, all substituents may be further substituted by 1-3 substituents chosen from alkyl, carboxy, $-COOR_2$ (wherein R_2 is the same as defined earlier), $-NR_xR_y$, $-C(=O)NR_xR_y$, $-OC(=O)NR_xR_y$, $-NHC(=O)NR_xR_y$, $-NHC(=O)OR_2$, (wherein R_x and R_y are the same as defined earlier), hydroxy, alkoxy, halogen, $-CF_3$, cyano, and $-S(O)_nR_1$ (where n and R_1 are the same as defined earlier).

Alkyl group as defined above may also be interrupted by 1-5 atoms of groups independently chosen from oxygen, sulfur and $-NR_a$ (where R_a is chosen from hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl).

The term "alkenyl" unless and otherwise specified refers to a monoradical of a branched or unbranched unsaturated hydrocarbon group preferably having from 2 to 20 carbon atoms with cis or trans geometry. Preferred alkenyl groups include ethenyl or vinyl, 1-propylene or allyl, iso-propylene, bicyclo[2.2.1]heptene, and the like. In the event that alkenyl is attached to the heteroatom, the double bond cannot be alpha to the heteroatom.

It may further be substituted with one or more substituents selected from the group consisting of alkyl, alkynyl, alkoxy, cycloalkyl, acyl, acylamino, acyloxy, $-CF_3$, $-NR_xR_y$, $-C(=O)NR_xR_y$, $-OC(=O)NR_xR_y$, $-NHC(=O)NR_xR_y$ (wherein R_x and R_y are the same as defined earlier), alkoxycarbonylamino, azido, cyano, halogen, hydroxy, thiocarbonyl, substituted thiocarbonyl, carboxy, $-COOR_2$ (wherein R_2 is the same as defined earlier), thiol, aryl, aralkyl, aryloxy, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl, alkoxyamino, nitro, $S(O)_nR_1$ (wherein n and R_1 are the same as defined earlier). Unless otherwise

constrained by the definition, all substituents may optionally be further substituted by 1-3 substituents chosen from alkyl, carboxy, -$COOR_2$ (wherein R_2 is the same as defined earlier), hydroxy, alkoxy, halogen, -CF_3, cyano, -NR_xR_y, -$C(=O)NR_xR_y$, -$OC(=O)NR_xR_y$ (wherein R_x and R_y are the same as defined earlier) and -$S(O)_nR_1$ (where R_1 and n are the same as defined earlier).

The term "alkynyl" unless and otherwise specified refers to a monoradical of an unsaturated hydrocarbon, preferably having from 2 to 20 carbon atoms. Preferred alkynyl groups include ethynyl, propargyl or propynyl, and the like. In the event that alkynyl is attached to the heteroatom, the triple bond cannot be alpha to the heteroatom. It may further be substituted with one or more substituents selected from the group consisting of alkyl, alkenyl, alkoxy, cycloalkyl, acyl, acylamino, alkoxyamino, acyloxy, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, thiocarbonyl, substituted thiocarbonyl, -CF_3, carboxy, -$COOR_2$ (wherein R_2 is the same as defined earlier), thiol, aryl, aralkyl, aryloxy, nitro, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl, -NR_xR_y, -$C(=O)NR_xR_y$, -$OC(=O)NR_xR_y$, -$NHC(=O)NR_xR_y$ (wherein R_x and R_y are the same as defined earlier), -$S(O)_nR_1$ (wherein n and R_1 are the same as defined earlier). Unless otherwise constrained by the definition, all substituents may optionally be further substituted by 1-3 substituents chosen from alkyl, carboxy, -$COOR_2$ (wherein R_2 is the same as defined earlier), hydroxy, alkoxy, halogen, -CF_3, -NR_xR_y, -$C(=O)NR_xR_y$, -$OC(=O)NR_xR_y$ (wherein R_x and R_y are the same as defined earlier), cyano and -$S(O)_nR_1$ (wherein R_1 and n are the same as defined earlier).

The term "cycloalkyl" refers to cyclic alkyl groups containing 3 to 20 carbon atoms having a single cyclic ring or multiple condensed rings, which may optionally contain one or more olefinic bonds, unless or otherwise constrained by the definition. Such cycloalkyl groups include, by way of example, single ring structures such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclopentenyl, and the like, or multiple ring structures such as adamantanyl, and bicyclo [2.2.1] heptane, or cyclic alkyl groups to which is fused with an aryl group, for example indane or tetrahydro-naphthalene and the like.
It may further be substituted with one or more substituents selected from the group consisting of alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, acyl, acylamino, alkoxyamino, acyloxy, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, thiocarbonyl, substituted thiocarbonyl, carboxy, -$COOR_2$ (wherein R_2 is the same as defined earlier), thiol, aryl, aralkyl, aryloxy, -NR_xR_y, -$NHC(=O)NR_xR_y$, -$C(=O)NR_xR_y$, -$OC(=O)NR_xR_y$ (wherein R_x and

R_y are the same as defined earlier), nitro, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl, $-CF_3$, $-S(O)_nR_1$ (wherein R_1 and n are the same as defined earlier). Unless otherwise constrained by the definition, all substituents may optionally be further substituted by 1-3 substituents chosen from alkyl, carboxy, hydroxy, alkoxy, halogen, CF_3, $-NR_xR_y$, $-C(=O)NR_xR_y$, $-NHC(=O)NR_xR_y$, $-OC(=O)NR_xR_y$ (wherein R_x and R_y are the same as defined earlier), cyano and $-S(O)_nR_1$ (where R_1 and n are the same as defined earlier).

The term "alkoxy" denotes the group O-alkyl wherein alkyl is the same as defined above.

The term "aralkyl" refers to aryl linked through alkyl (wherein alkyl is the same as defined above) portion and the said alkyl portion contains carbon atoms from 1-6 and aryl is as defined below.

The term "aryl" herein refers to a carbocyclic aromatic group, (for example, phenyl, biphenyl or naphthyl ring and the like optionally substituted with 1 to 3 substituents selected from the group consisting of halogen (F, Cl, Br, I), hydroxy, alkyl, alkenyl, acylamino, alkoxyamino, thiocarbonyl, substituted thiocarbonyl, alkynyl, alkoxycarbonylamino, cycloalkyl, alkoxy, acyl, aryloxy, cyano, $-CF_3$, nitro, $-NR_xR_y$, $-C(=O)NR_xR_y$, $-C(=NOH)NH_2$, $-NHC(=O)NR_xR_y$, $-OC(=O)NR_xR_y$ (wherein R_x and R_y are the same as defined earlier), carboxy, $-S(O)_nR_1$ (where R_1 and n are the same as defined earlier), $-COOR_2$ (wherein R_2 is the same as defined earlier), heterocyclyl, heteroaryl, heterocyclylalkyl or heteroarylalkyl.

The term "carboxy" as defined herein refers to –C(=O)OH.

The term "aryloxy" denotes the group O-aryl, wherein aryl is as defined above.

The term "heteroaryl" unless and otherwise specified refers to monocyclic aromatic ring structure containing 5 or 6 carbon atoms, a bicyclic or a tricyclic aromatic group having 8 to 10 carbon atoms, with one or more heteroatom(s) independently selected from the group consisting of N, O and S optionally substituted with 1 to 3 substituent(s) selected from the group consisting of halogen (F, Cl, Br, I), hydroxy, alkyl, alkenyl, alkynyl, acylamino, thiocarbonyl, substituted thiocarbonyl, alkoxyamino, alkoxycarbonylamino, cycloalkyl, acyl, heteroaryl, heterocyclyl, heterocyclylalkyl, heteroarylalkyl, carboxy, $-S(O)_nR_1$ (where R_1 and n are the same as defined earlier), $-CF_3$, $-COOR_2$ (wherein R_2 is the same as defined earlier), aryl, alkoxy, aralkyl, cyano, nitro, $-NR_xR_y$, $-C(=O)NR_xR_y$, -

$NHC(=O)NR_xR_y$ and $-OC(=O)NR_xR_y$ (wherein R_x and R_y are the same as defined earlier). Examples of heteroaryl groups are pyridinyl, pyridazinyl, pyrimidinyl, pyrrolyl, oxazolyl, thiazolyl, thienyl, isoxazolyl, triazinyl, furanyl. pyrazolyl, imidazolyl, benzimidazolone, pyrazolone, benzofuranyl, indolyl, benzothiazolyl, xanthene, benzoxazolyl, and the like.

The term "heterocyclyl" unless and otherwise specified refers to a non aromatic monocyclic, bicyclic (fused, bridged, or spiro) or tricyclic cycloalkyl group having 5 to 10 atoms in which 1 to 3 carbon atoms in a ring are replaced by heteroatoms selected from the group comprising of O, S and N, and are optionally benzofused or fused heteroaryl of 5-6 ring members and the said heterocyclyl group is optionally substituted wherein the substituents are selected from the group consisting of halogen (F, Cl, Br, I), hydroxy, alkyl, alkenyl, alkynyl, cycloalkyl, acyl, thiocarbonyl, substituted thiocarbonyl, aryl. alkoxy, aralkyl, heteroaryl, heterocyclyl, heterocyclylalkyl, heteroarylalkyl, cyano, alkoxyamino, acylamino, alkoxycarbonylamino, nitro, $-CF_3$, carboxy, $-S(O)_nR_1$ (where R_1 and n are the same as defined earlier), $-COOR_2$ (wherein R_2 is the same as defined earlier), $-NHC(=O)NR_xR_y$, $-C(=O)NR_xR_y$, $-OC(=O)NR_xR_y$ (wherein R_x and R_y are the same as defined earlier). Examples of heterocyclyl groups are tetrahydrofuranyl, dihydrofuranyl, dihydropyridinyl, isoxazolinyl, piperidinyl, morpholine, piperazinyl, dihydrobenzofuryl, azabicyclohexyl, azabicyclooctyl, dihydroindolyl, and the like.

"Heteroarylalkyl" refers to heteroaryl (wherein heteroaryl is same as defined earlier) linked through alkyl (wherein alkyl is the same as defined above) portion and the said alkyl portion contains carbon atoms from 1-6.

"Heterocyclylalkyl" refers to heterocyclyl (wherein heterocyclyl is same as defined earlier) linked through alkyl (wherein alkyl is the same as defined above) portion and the said alkyl portion contains carbon atoms from 1-6.

"Acyl" refers to $-C(=O)R''$ wherein R'' is selected from the group hydrogen, alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl or heterocyclylalkyl.

"Thiocarbonyl" refers to -C(=S)H.

"Substituted thiocarbonyl" refers to -C(=S)R", whercin R" is selected from alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl or heterocyclylalkyl, amine or substituted amine.

The term "leaving group" generally refers to groups that exhibit the desirable properties of being labile under the defined synthetic conditions and also, of being easily separated from synthetic products under defined conditions. Examples of such leaving groups includes but not limited to halogen (F, Cl, Br, I), triflates, tosylate, mesylates, hydroxy radicals and the like.

The term "Protecting Groups" is used herein to refer to known moieties, which have the desirable property of preventing specific chemical reaction at a site on the molecule undergoing chemical modification intended to be left unaffected by the particular chemical modification. Also the term protecting group, unless or other specified may be used with groups such as hydroxy, amino, carboxy and example of such groups are found in T.W. Greene and P.G.M. Wuts, "Protective Groups in Organic Synthesis", 2nd Edn. John Wiley and Sons, New York, N.Y., which is incorporated herein by reference. The species of the carboxylic protecting groups, amino protecting groups or hydroxy protecting group employed is not so critical so long as the derivatised moiety/moieties is/are stable to conditions of subsequent reactions and can be removed at the appropriate point without disrupting the remainder of the molecule.

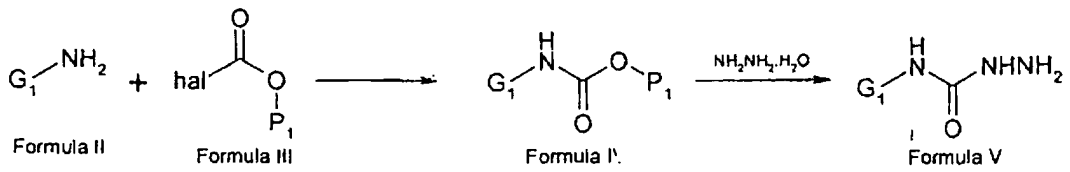
The term "pharmaceutically acceptable salts" refers to derivatives of compounds that can be modified by forming their corresponding acid or base salts. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acids salts of basic residues (such as amines), or alkali or organic salts of acidic residues (such as carboxylic acids), and the like.

DETAILED DESCRIPTION OF THE INVENTION

The compounds of the present invention may be prepared by techniques well known in the art and familiar to a practitioner skilled in art of this invention. In addition, the compounds of the present invention may be prepared by the process described herein, this process is not the only means by which the compounds described may be synthesised. Further, the various

synthetic steps described herein may be performed in an alternate sequence in order to give the desired compounds.

Scheme I



The compounds of Formulae IV and V can be prepared by following the procedure as depicted in scheme I. Thus a compound of Formula II (G_1 is the same as defined earlier) is reacted with a compound of Formula III [hal is Cl, Br or I and P_1 is aryl (such as phenyl or p-nitrophenyl)] to give a compound of Formula IV, which is reacted with hydrazine monohydrate to give a compound of Formula V.

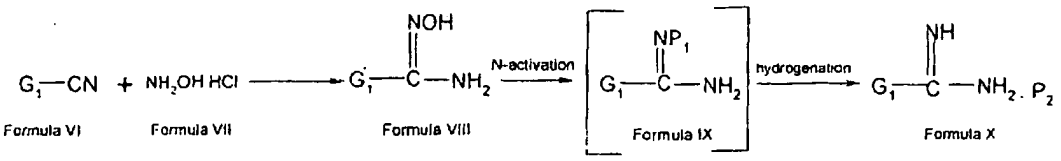
The reaction of a compound of Formula II with a compound of Formula III to give a compound of Formula IV can be carried out in an organic solvent selected from dichloroethane, dichloromethane, chloroform or carbon tetrachloride in the presence of a

base selected from pyridine, N-methylmorpholine, triethylamine or diisopropylethylamine.

The reaction of a compound of Formula IV with hydrazine monohydrate to give a compound of Formula V can be carried out in an organic solvent selected from dioxane, ethanol, tetrahydrofuran, diethylether or dimethylformamide.
Alternatively, one may also use hydrazine sulphate or hydrazine in place of hydrazine monohydrate.

The compounds prepared by following scheme I are:
Phenyl (4-fluorophenyl)carbamate
N-(4-Fluorophenyl)hydrazinecarboxamide

Scheme II



The compounds of Formulae VIII and X can be prepared by following the reaction sequence as depicted in scheme II. Thus a compound of Formula VI (wherein G_1 is the same as defined earlier) is reacted with a compound of formula VII to give a compound of Formula VIII, which undergoes N-activation to give a compound of Formula IX (*in-situ*) (wherein P_1 represents N-activating groups selected form acetyl, propionyl or trifluoro acetyl), which further undergoes hydrogenation to give a salt of Formula X (wherein P_2 is acetic acid, propionic acid or trifluoroacetic acid).

The reaction of a compound of formula VI with a compound of Formula VII to give compound of Formula VIII can be carried out in presence of a base selected from sodium carbonate, lithium carbonate or potassium carbonate in water and in an organic solvent selected from ethanol, methanol, propanol or isopropylalcohol.

The N-activation of compounds of Formula VIII to give a compound of Formula IX (*in–situ*) can be carried out with N-activating agents selected from acetic acid, propionic acid or trifluoroacetic acid in the presence of corresponding anhydride selected from acetic anhydride, propionic anhydride or trifluoroacetic anhydride.

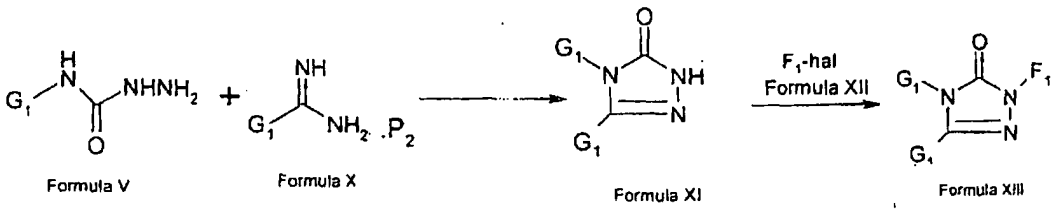
The hydrogenation of a compound of Formula IX to give a compound of Formula X can be carried out under hydrogenating conditions, selected from palladium on carbon or for example, under catalytic transfer hydrogenation conditions of ammonium formate and palladium on carbon.

The compounds prepared following scheme II are:

N'-Hydroxypyridine-4-carboximidamide

Pyridine-4-carboximidamide acetate

Scheme III



The compound of Formula XIII can be prepared by following the reaction sequence as depicted in the scheme III. Thus a compound of Formula V (wherein G_1 is the same as defined earlier) is reacted with compound of Formula X to give compound of Formula XI, which is reacted with a compound of Formula XII (wherein F_1 is alkyl, cycloalkyl or aryl and hal is Cl, Br or I) to give compound of Formula XIII.

The reaction of a compound of Formula V with compound of Formula X to give a compound of Formula XI can be carried out in an organic solvent selected from dimethylformamide, dimethylsulphoxide, tetrahydrofuran, diethyl ether or dioxane in the presence of protonating agent selected from acetic acid.

The reaction of compound of Formula XI with compound of Formula XII to give a compound of Formula XIII (when F_1 is aryl) can be carried out in an organic solvent selected from dioxane, tetrahydrofuran, diethyl ether or dimethylformamide in the presence of a base selected from potassium carbonate, potassium phosphate, cesium carbonate, lithium carbonate or sodium carbonate and catalyst selected from copper iodide or palladium (0) or palladium (II) in combination with triphenylphosphine.

The reaction of compound of Formula XI with compound of Formula XII to give a compound of Formula XIII (when F_1 is alkyl or cycloalkyl) can be carried out in an organic solvent selected from dimethylformamide, dioxane, tetrahydrofuran or diethyl ether in the presence of a base selected from potassium carbonate, cesium carbonate, lithium carbonate or sodium carbonate.

Particular compounds are mentioned below

4-(4-Fluorophenyl)-5-pyridin-4-yl-2-[4-(1*H*-tetrazol-5-yl)phenyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 1),

4-[4-(4-Fluorophenyl)-5-oxo-3-pyridin-4-yl-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]-*N*'-hydroxybenzenecarboximidamide (Compound No. 2),

4-[4-(4-Fluorophenyl)-5-oxo-3-pyridin-4-yl-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]benzonitrile (Compound No. 3),

4-(4-Fluorophenyl)-2-(4-methoxyphenyl)-5-pyridin-4-yl-2,4-dihydro-3*H*-1,2,4-triazol-3- one (Compound No. 4),

2-(4-Chlorophenyl)-4-(4-fluorophenyl)-5-pyridin-4-yl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 5),

2-(2,4-Difluorophenyl)-4-(4-fluorophenyl)-5-pyridin-4-yl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 6),

4-(4-Fluorophenyl)-2-(4-methylphenyl)-5-pyridin-4-yl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 7),

2-Cycloheptyl-4-(4-fluorophenyl)-5-pyridin-4-yl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 8),

2-Cyclohexyl-4-(4-fluorophenyl)-5-pyridin-4-yl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 9),

2-(Cyclopropylmethyl)-4-(4-fluorophenyl)-5-pyridin-4-yl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 10),

4-(4-Fluorophenyl)-2-(2-morpholin-4-ylethyl)-5-pyridin-4-yl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 11),

2-(Cyclohexylmethyl)-4-(4-fluorophenyl)-5-pyridin-4-yl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No.12),

2-Cyclopentyl-4-(4-fluorophenyl)-5-pyridin-4-yl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 13),

4-(4-Fluorophenyl)-2-(2-piperidin-1-ylethyl)-5-pyridin-4-yl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No.14),

2-[4-(4-Fluorophenyl)-5-oxo-3-pyridin-4-yl-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]acetamide (Compound No. 15),

4-[4-(4-Fluorophenyl)-5-oxo-3-phenyl-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]-2-methylbenzonitrile (Compound No. 16),

2-(4-Chlorophenyl)-4-(4-fluorophenyl)-5-phenyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 17),

(4-(4-Fluorophenyl)-2-(4-methylphenyl)-5-phenyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 18),

4-(4-Fluorophenyl)-2-(4-methoxyphenyl)-5-phenyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 19),

4-(4-Fluorophenyl)-2,5-diphenyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 20),

2-(2,4-Difluorophenyl)-4-(4-fluorophenyl)-5-phenyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 21),

4-(4-Fluorophenyl)-2-(4-nitrophenyl)-5-phenyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 22),

4-(4-Fluorophenyl)-2-(2-morpholin-4-ylethyl)-5-phenyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 23),

4-(4-Fluorophenyl)-5-phenyl-2-(2-piperidin-1-ylethyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 24),

4-(4-Fluorophenyl)-5-phenyl-2-(3-piperidin-1-ylpropyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 25).

Examples set forth demonstrates the general synthetic procedure for the preparation of representative compounds. The examples are provided to illustrate particular aspect of the disclosure and should not be constrained to limit the scope of the present invention.

Experimental

Scheme I, procedure:

Example 1: Synthesis of *N*-(4-fluorophenyl)hydrazinecarboxamide (Formula V)

Step *a*: Phenyl (4-fluorophenyl)carbamate

To a cold solution of 4-fluoroaniline (11.73g, 105.56mmol) at 0°C in 1,2-dichloroethane (50ml) was added pyridine (12.5g, 158.34mmol) and stirred for 15 minutes. To the resulting reaction mixture was added phenyl chloroformate (19.87ml, 158.34mmol) dropwise and stirred at the same temperature for 2 hrs. The organic solvent was evaporated under reduced pressure followed by removal of pyridine azeotropically by addition of toluene. To the residue thus obtained was added water and stirred till a solid title compound was obtained. Yield =12.0g.

Step *b*: *N*-(4-fluorophenyl)hydrazinecarboxamide

To the solution of the compound obtained from step *a* above (12g, 51.95mmoles) in 1,4-dioxane (60ml) was added hydrazine hydrate (6.5g, 129.87mmol) and refluxed for approx. 2.5 hours. The solvent was evaporated under reduced pressure followed by addition of dichloromethane and hexane. A white solid was separated out which was filtered, washed with hexane and dried under reduced pressure to furnish the title compound. Yield = 8g.

Scheme II, procedure:

Example 2: Synthesis of pyridine-4-carboximidamide acetate (Formula IX)

Step *a*: *N'*-hydroxypyridine-4-carboximidamide

The compounds 4-pyridyl carbonitrile (commercially available) (25g, 240.13mmoles), hydroxylamine hydrochloride (61.24g, 881.28mmoles) and sodium carbonate (43.77g,

413.02mmoles) were dissolved in a solution of water (125ml) and ethanol (375ml). The reaction mixture was then stirred for 10 minutes at room temperature followed by refluxing for 17 hrs. The resulting reaction mixture was cooled to room temperature and diluted with ice-cold water. The precipitate thus obtained were collected by filtration, washed with water and dried under *vacuum* to furnish the title compound.

Yield = 30g.

Step *b*: Pyridine-4-carboximidamide acetate

The compound obtained from step *a* above (145.98mmoles, 20g) was dissolved in glacial acetic acid (100ml) and acetic anhydride (218.98mmoles, 20.64ml) and stirred for 5 minutes. To the resulting reaction mixture was added palladium on carbon (10g, 10%) and hydrogenated at 45-50 psi for 2hrs. The mixture was filtered through celite pad and washed with glacial acetic acid. The filtrate was concentrated under reduced pressure and excess glacial acetic acid was removed by co-evaporating the residue with n-heptane for approximately four times to furnish the title compound. Yield: 18g.

Scheme III, procedure:

Example 3: Synthesis of 4-(4-fluorophenyl)-5-pyridin-4-yl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Formula X)

To a mixture of *N*-(4-fluorophenyl)hydrazinecarboxamide (6g, 25.947mmol) and pyridine-4-carboximidamide acetate (18.8g, 103.89mmol) was added dry dimethylformamide (60ml) under nitrogen atmosphere and cooled to 0°C. To the resulting reaction mixture was added glacial acetic acid (30ml) and stirred for 30 minutes at the same temperature and then at 110°C for 5 hours under nitrogen atmosphere. The solvent was evaporated under reduced pressure followed by addition of saturated sodium bicarbonate solution. The solid thus obtained was filtered and mother liquor was extracted with ethyl acetate. The solvent was evaporated under reduced pressure and the residue thus obtained was purified by column chromatography using ethyl acetate in hexane (2:8) as eluent to furnish the title compound. Yield: 1g.

Example 4: Synthesis of 4-(4-fluorophenyl)-2-(4-methylphenyl)-5-pyridin-4-yl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 7)

To a mixture of the compound obtained from Example 3 (0.10g, 0.390mmol), potassium carbonate (0.108g, 0.78mmol) and copper iodide (0.015g, 0.07mmol) under argon atmosphere was added dry dioxane (5ml), (±)-*trans* cyclohexane diamine (10mol%) and 4-

bromo toluene (0.134g, 0.78mmol) and stirred for 15 hours at 110°C. The resulting reaction mixture was cooled to room temperature followed by quenching with ethyl acetate. The mixture was filtered through celite pad. The filtrate was concentrated under reduced pressure and the residue thus obtained was purified by column chromatography using ethyl acetate in hexane (2:8) as eluent to furnish the title compound. Yield: 0.09g.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.62 (2H, d, J=8.00Hz, Ar-*H*), 7.94 (2H, d, J=8.00Hz, Ar-*H*), 7.33-7.27 (6H, m, Ar-*H*), 7.22-7.19 (2H, m, Ar-*H*) and 2.39 (3H, s, Ar-CH_3).

Mass spectrum (*m/z*, +ve ion mode): 347[M^++1].

Following analogues were prepared similarily,

4-(4-Fluorophenyl)-5-pyridin-4-yl-2-[4-(1*H*-tetrazol-5-yl)phenyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 1)

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.64 (2H, d, J=6.00Hz, Ar-*H*), 8.17 (4H, s, Ar-*H*), 7.61-7.58 (2H, m, Ar-*H*), 7.43-7.36 (2H, m, Ar-*H*) and 7.35 (2H, d, J=1.60Hz, Ar-*H*).

Mass spectrum (*m/z* +ve ion mode): 401[M^++1].

4-[4-(4-Fluorophenyl)-5-oxo-3-pyridin-4-yl-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]-*N*'-hydroxybenzenecarboximidamide (Compound No. 2)

^{1}H NMR (400 MHz, DMSO-d_6): δ 9.69 (1H, s, N-*OH* & D_2O exchangeable), 8.64 (2H, d, J=5.60Hz, Ar-*H*), 8.03 (2H, d, J=8.80Hz, Ar-*H*), 7.83 (2H, d, J=8.80Hz, Ar-*H*), 7.62-7.56 (3H, m, Ar-*H*), 7.43-7.34 (3H, m, Ar-*H*) and 5.87 (2H, brs, NH_2 & D_2O exchangeable).

Mass spectrum (*m/z*, +ve ion mode): 391[M^++1].

4-[4-(4-Fluorophenyl)-5-oxo-3-pyridin-4-yl-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]benzonitrile (Compound No. 3)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.66 (2H, s, Ar-*H*), 8.30 (2H, d=8.80Hz, Ar-*H*), 7.80 (2H, d, J=8.80Hz, Ar-*H*), 7.76-7.30 (2H, m, Ar-*H*) and 7.33-7.21 (4H, m, Ar-*H*).

Mass spectrum (*m/z*, +ve ion mode): 358[M^++1].

IR spectrum (KBr): 3377, 2223, 1713, 1602, 1508 and 1373 cm^{-1}.

4-(4-Fluorophenyl)-2-(4-methoxyphenyl)-5-pyridin-4-yl-2,4-dihydro-3*H*-1,2,4-triazol-3- one (Compound No. 4)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.62 (2H, d, J=6.00Hz, Ar-*H*), 7.95 (2H, d, J=9.20Hz, Ar-*H*), 7.33-7.02 (6H, m, Ar-*H*), 7.00 (2H, d, J=9.20Hz, Ar-*H*) and 3.86 (3H, s, Ar-OCH_3).
Mass spectrum (*m/z*, +ve ion mode): 362[M^++1].

2-(4-Chlorophenyl)-4-(4-fluorophenyl)-5-pyridin-4-yl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 5)
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.64 (2H, d, J=4.00Hz, Ar-*H*), 8.06 (2H, d, J=8.00Hz, Ar-*H*), 7.44 (2H, d, J=8.00Hz, Ar-*H*) and 7.33-7.20 (6H, m, Ar-*H*).
Mass spectrum (*m/z*, +ve ion mode): 369[M^++1+2] and 367[M^++1].
IR spectrum (KBr): 3448, 1706, 1601, 1495 and 1376 cm^{-1}.

2-(2,4-Difluorophenyl)-4-(4-fluorophenyl)-5-pyridin-4-yl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 6)
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66-7.60 (1H, m, Ar-*H*), 7.34-7.19 (8H, m, Ar-*H*) and 7.07-7.02 (2H, m, Ar-*H*).
Mass spectrum (*m/z*, positive ion mode): 369[M^++1].

4-[4-(4-Fluorophenyl)-5-oxo-3-phenyl-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]-2-methylbenzonitrile (Compound No. 16)
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.16-8.10 (2H, m, Ar-*H*), 7.69 (2H, d, J=9.00Hz, Ar-*H*), 7.46-7.36 (6H, m, Ar-*H*), 7.19-7.14 (2H, m, Ar-*H*) and 2.61 (3H, s, Ar-CH_3).
Mass spectrum (*m/z*, +ve ion mode): 371[M^++1]
IR spectrum (KBr): 3431, 2215, 1719, 1609, 1511 and 1365 cm^{-1}

2-(4-Chlorophenyl)-4-(4-fluorophenyl)-5-phenyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 17)
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.05 (2H, d, J=9.00Hz, Ar-*H*), 7.42-7.24 (9H, brm, Ar-*H*) and 7.15-7.10 (2H, m, Ar-*H*).
Mass spectrum (*m/z*, +ve ion mode): 368[M^++1+2] and 366[M^++1].
IR spectrum (KBr): 3456, 1709, 1491, 1375, 1231 and 1153 cm^{-1}.

(4-(4-Fluorophenyl)-2-(4-methylphenyl)-5-phenyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 18)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.94-7.91 (2H, m, Ar-*H*), 7.41-7.27 (9H, m, Ar-*H*), 7.17-7.11 (2H, m, Ar-*H*) and 2.38 (3H, s, Ar-CH_3).

Mass spectrum (*m/z*, +ve ion mode): 346[M^++1].

IR spectrum (KBr): 3450, 1706, 1515, 1379 and 1153 cm^{-1}.

4-(4-Fluorophenyl)-2-(4-methoxyphenyl)-5-phenyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 19)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.96 (2H, d, J=9.00Hz, Ar-*H*), 7.41-7.30 (4H, m, Ar-*H*), 7.17-7.11 (3H, m, Ar-*H*), 7.00 (2H, m, Ar-*H*), 7.00 (2H, d, J=6.00Hz, Ar-*H*) and 3.84 (3H, s, Ar-OCH_3).

Mass spectrum (*m/z*, +ve ion mode): 362[M^++1]

IR spectrum (KBr): 3449, 1706, 1513, 1247 and 1156 cm^{-1}.

4-(4-Fluorophenyl)-2,5-diphenyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 20)

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.10 (2H, d, J=6.00Hz, Ar-*H*), 7.49-7.37 (7H, brm, Ar-*H*), 7.35-7.18 (3H, brm, Ar-*H*) and 7.15-7.12 (2H, m, Ar-*H*).

Mass spectrum (*m/z*, +ve ion mode): 332[M^++1].

2-(2,4-Difluorophenyl)-4-(4-fluorophenyl)-5-phenyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 21)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43-7.34 (1H, brm, Ar-*H*), 7.32-7.27 (7H, brm, Ar-*H*), 7.17-7.11 (2H, brm, Ar-*H*) and 7.05-6.99 (2H, brm, Ar-*H*).

Mass spectrum (*m/z*, +ve ion mode): 368[M^++1].

4-(4-Fluorophenyl)-2-(4-nitrophenyl)-5-phenyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 22)

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.36-8.26 (4H, brm, Ar-*H*) and 7.55-7.15 (9H, brm, Ar-*H*).

Mass spectrum (*m/z*, +ve ion mode): 378[M^++1].

Example 5: Synthesis of 2-(cyclohexylmethyl)-4-(4-fluorophenyl)-5-pyridin-4-yl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No.12)

To a solution of the compound obtained from Example 3 above (0.080g, 0.312mmol) in dry dimethylformamide (2ml) was added potassium carbonate (0.130g, 0.938 mmol) and stirred

for 10 minutes. To the resulting reaction mixture was added cyclohexylmethyl bromide (0.111g, 0.625mmol) and stirred at 80°C for 8-10 hours. The reaction mixture was poured into water, extracted with ethyl acetate, washed with water, dried over anhydrous sodium sulphate, filtered and evaporated under reduced pressure. The residue thus obtained was purified by column chromatography using ethyl acetate in hexane (2:3) as eluent to furnish the title compound. Yield: 0.040g.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.57 (2H, d, J=4.00Hz, Ar-*H*), 7.25-7.14 (6H, m, Ar-*H*), 3.76 (2H, d, J=4.00Hz, -NCH_2), 1.77-1.74 (1H, m, -*CH*), 1.69-1.67 (6H, m, 3× -CH_2) and 1.33-1.28 (4H, m, 2×-CH_2).

Mass spectrum (*m/z*, +ve ion mode): 353[M^++1].

Following analogues were prepared similarily,

2-Cycloheptyl-4-(4-fluorophenyl)-5-pyridin-4-yl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 8)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.57 (2H, d, J=8.00Hz, Ar-*H*), 7.27-7.15 (6H, m, Ar-*H*), 4.44-4.41 (1H, m, -N*CH*), 2.07-2.03 (4H, m, 2×-CH_2), 1.69-1.65 (2H, m, -CH_2) and 1.64-1.59 (6H, m, 3×-CH_2).

Mass spectrum (*m/z*, +ve ion mode): 353[M^++1].

2-Cyclohexyl-4-(4-fluorophenyl)-5-pyridin-4-yl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 9)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56 (2H, d, J=8.00Hz, Ar-*H*), 7.27-7.15 (6H, m, Ar-*H*), 4.23-4.19 (1H, m, -N*CH*), 2.02-1.83 (6H, m, 3×-CH_2) and 1.46-1.25 (4H, m, 2×-CH_2).

Mass spectrum (*m/z*, +ve ion mode): 339[M^++1].

2-(Cyclopropylmethyl)-4-(4-fluorophenyl)-5-pyridin-4-yl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 10)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (2H, brs, Ar-*H*), 7.27-7.20 (6H, m, Ar-*H*), 3.75 (2H, d, J=12.00Hz, -NCH_2), 2.96 (1H, m, -*CH*) and 1.35-1.30 (4H, m, 2×-CH_2).

Mass spectrum (*m/z*, +ve ion mode): 311[M^++1].

4-(4-Fluorophenyl)-2-(2-morpholin-4-ylethyl)-5-pyridin-4-yl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 11)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.58 (2H, d, J=4.00Hz, Ar-*H*), 7.25-7.16 (6H, m, Ar-*H*), 4.08 (2H, t, J=8.00Hz, -OCH_2), 3.72-3.70 (4H, brm, -OCH_2 & -NCH_2), 2.83 (2H, t, J=8.00Hz, -NCH_2) and 2.58 (2H, brm, -NCH_2).

Mass spectrum (*m/z*, +ve ion mode): 370[M^++1].

2-Cyclopentyl-4-(4-fluorophenyl)-5-pyridin-4-yl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 13)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56 (2H, d, J=4.00Hz, Ar-*H*), 7.25-7.15 (6H, m, Ar-*H*), 4.79-4.73 (1H, m, -*CH*), 2.12-2.01 (6H, m, 3×-CH_2) and 2.00-1.91 (2H, m, -CH_2).

Mass spectrum (*m/z*, +ve ion mode): 325[M^++1].

4-(4-Fluorophenyl)-2-(2-piperidin-1-ylethyl)-5-pyridin-4-yl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No.14)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.54 (2H, d, J=4.00Hz, Ar-*H*), 7.23-7.21 (4H, m, Ar-*H*), 7.18-7.15 (2H, m, Ar-*H*), 4.06 (2H, t, J=8.00Hz, -NCH_2), 2.80 (2H, brm, -NCH_2), 2.50 (4H, brm, 2×-NCH_2) and 1.64-1.57 (6H, brm, 3×-CH_2).

Mass spectrum (*m/z*, +ve ion mode): 368[M^++1].

2-[4-(4-Fluorophenyl)-5-oxo-3-pyridin-4-yl-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]acetamide (Compound No. 15)

^{1}H NMR (400 MHz, $CDCl_3$+MeOD): δ 8.54 (2H, d, J=8.00Hz, Ar-*H*), 7.48-7.21 (7H, m, Ar-*H* & -N*H*) and 4.66 (2H, s, -CH_2CO).

Mass spectrum (*m/z*, +ve ion mode): 314[M^++1].

IR spectrum (KBr): 3422, 1686, 1623, 1507 and 1219 cm^{-1}.

4-(4-Fluorophenyl)-2-(2-morpholin-4-ylethyl)-5-phenyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 23)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39-7.08 (9H, brm, Ar-*H*), 4.06 (2H, t, J=6.00Hz, -NCH_2), 3.72-3.69 (4H, m, 2×-OCH_2), 2.83 (2H, t, J=6.00Hz, -NCH_2) and 2.59-2.56 (4H, m, 2×-NCH_2).

Mass spectrum (*m/z*, +ve ion mode): 369[M^++1].

4-(4-Fluorophenyl)-5-phenyl-2-(2-piperidin-1-ylethyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 24)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.52-7.50 (1H, m, Ar-*H*), 7.37-7.07 (8H, m, Ar-*H*), 4.10 (2H, t, J=6.00Hz, -NCH_2), 4.05 (2H, t, J=6.00Hz, -NCH_2), 2.89-2.78 (2H, m, -NCH_2), 2.57-2.52 (4H, brm, -NCH_2&-CH_2), 2.41-2.36 (2H, brm, -CH_2) and 1.45-1.44 (2H, brm, -CH_2).

Mass spectrum (*m/z*, +ve ion mode): 367[M^++1].

4-(4-Fluorophenyl)-5-phenyl-2-(3-piperidin-1-ylpropyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 25)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38-7.21 (7H, brm, Ar-*H*), 7.17-7.08 (2H, m, Ar-*H*), 3.97 (2H, t, J=6.00Hz, -NCH_2), 2.77-2.72 (6H, brm, 3×-NCH_2), 1.74-1.71 (4H, m, 2×-CH_2), 1.52-1.50 (2H, m, -CH_2) and 1.35-1.33 (2H, m, -CH_2).

Mass spectrum (*m/z*, +ve ion mode): 381[M^++1].

Example 6: *p38 Inhibition Assay*

p38 MAP Kinase inhibitory potential was evaluated utilizing the proprietary IQ technology (Pierce Biotechnology). The assay incorporates an iron-containing compound that binds specifically to phosphate groups present on fluorescent dye-labeled phosphorylated peptides which in this case was the Epidermal Growth Factor Receptor Peptide (KRELVEPLTPSGEAPNQALLR). Recombinant activated GST- p38MAP kinase-α was used at a concentration of 40nM. The reaction was initiated with 100μM ATP. When bound to the phosphate group, the iron-containing compound was brought into proximity to the flurophore and act as a dark quencher of the fluorescent dye. Results were quantitated by comparing the observed relative fluorescence units of test samples to blanks containing no enzyme. A dose response curve was generated with different concentrations of inhibitor and the IC50 was calculated using Graph Pad Prism.

The compounds disclosed herein showed p38 inhibitory activity in low μM range.

Dated this 29TH day of April, 2005.

For Ranbaxy Laboratories Limited

(SUSHIL KUMAR PATAWARI)
Company Secretary

ABSTRACT

TRIAZOLONE DERIVATIVES AS ANTI-INFLAMMATORY AGENTS

The present invention relates to novel triazolone derivatives as anti-inflammatory agents useful for inhibition and prevention of inflammation and associated pathologies including inflammatory and autoimmune diseases such as sepsis, rheumatoid arthritis, inflammatory bowel disease, type-1 diabetes, asthma, chronic obstructive pulmonary disorder, organ transplant rejection and psoriasis.

This invention also relates to pharmacological compositions containing the compounds of the present invention.